43 ~~45~~ ~~55~~. (Added) The method of claim ~~40~~ 38, wherein said at least one antibody is a polyclonal antibody preparation, or fragments of a polyclonal antibody preparation that specifically bind to said soluble receptors for tumor necrosis factors α and β.

44 ~~46~~ ~~56~~. (Added) The method of claim ~~40~~ 38, wherein the ~~biological fluid~~ whole blood is in contact with a plurality of antibodies comprising a mixture of different polyclonal antibody preparations or fragments thereof, wherein said polyclonal antibodies or fragments thereof specifically bind to said soluble receptors for tumor necrosis factors α and β.

REMARKS

Amendments to the Specification:

Applicants have amended the specification to correct two obvious typographical errors. On page 11, line 28 and page 17, line 18, the phrases are discussing antibodies and refer to "fractions" thereof. Applicants submit that in both lines, this term should be "fragments" and not "fractions." As set forth elsewhere in the specification, such as in original Claims 18-23 and 25-27, it is intended that the reference be to antibodies and "fragments" thereof. Applicants submit that the term "fraction" does not make sense with regard to a portion of an antibody and that one of skill in the art would know that the term "fragment" was intended.

Claim Amendments:

Applicants note that the claims have been amended to more particularly describe the present invention. In particular, the subject matter as set forth in original Claims 35, 36 and 39 has been moved into Claim 1. Support for the amendment to Claim 42 can be found in original Claims 2, 16-27 and 43. New Claims 50-56 have also been added to further describe the present invention. Support for Claim 50 can be found in original Claims 1, 10, 16-27, 36 and 42. Support for Claims 51-57 is found in the original claims as follows, with the original claims indicated in parentheses: Claim 51 (Claim 2); Claim 52 (Claim 3); Claim 53 (Claims 16 and 18); Claim 54 (Claims 20 and 22); Claim 55 (Claims 24 and 25); and Claim 56 (Claims 26 and 27). Support for other claim amendments is indicated in the comments below. It is noted that due to various amendments made to other claims, that Claims 35, 36, 39 and 43 have been canceled without prejudice to or disclaimer of the subject matter therein.

Non-elected Claims:

Applicants have canceled non-elected Claims 44-49, without prejudice to or disclaimer of the subject matter therein. Applicants expressly reserve their right to file a divisional application directed to the subject matter of Claims 44-49 without the need to file a terminal disclaimer. With regard to non-elected species, Applicants defer the cancellation of non-elected species until a final determination regarding patentability of the generic claim has been made.

Objection to the Claims:

The Examiner has objected to Claims 10 and 11 as claiming non-elected species. The Examiner has requested correction.

Since Claims 10 and 11 contain subject matter directed to a non-elected species, Applicants will respectfully defer amending Claims 10 and 11 in this regard until prosecution has concluded with regard to the elected species and examination of generic claims.

Rejection of Claims 1-3, 5, 10-27 and 34-43 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claims 1-3, 5, 10-27 and 34-43 under 35 U.S.C. § 112, second paragraph, contending that the claims are indefinite as set forth below.

a. The Examiner contends that Claims 1-3, 5, 12-27 and 34-43 are indefinite for reciting "targeted immune system inhibitor," in that it is allegedly not clear what group or groups of molecules are included in the group of immune system inhibitors.

Applicants traverse the Examiner's contention that the phrase "targeted immune system inhibitor" is indefinite. To the contrary, the specification describes immune system inhibitors in significant detail, including by providing several examples of specific immune system inhibitors, the inhibition of which is expected to result in an increase in a desirable immune response (e.g., page 4, line 10 to page 9, line 5). Furthermore, page 14, line 25 to page 15, line 2, states that the phrase refers to "a soluble mediator that decreases the magnitude of an immune response, or which discourages the development of particular immune mechanisms that are more effective in resolving a specific pathological condition, or which encourages the development of particular immune mechanisms that are less effective in resolving a specific pathological condition." Therefore, a particular immune system inhibitor is targeted by the method of the present invention because that inhibitor has a negative (i.e., inhibitory) effect on a desired immune response by inhibiting a

particular immune system stimulator or its actions, such that removal of the inhibitor would increase the action of the stimulator and therefore increase the desired immune response. The selection of the immune system inhibitor to be targeted will depend on the particular condition to be treated and the desired immune response to be stimulated, but such elements are well within the ability of one of skill in the art to determine, given the guidance provided in the specification.

b. The Examiner contends that Claims 10 and 11 are indefinite for being structured as improper Markush claims.

Claims 10 and 11 have been amended to use the proper Markush format.

c. The Examiner contends that Claim 11 is indefinite for reciting "homologues" in that it is allegedly not clear what compounds are encompassed by the term.

Applicants have amended Claim 11 to more particularly describe that the homologues are molecules produced by microorganisms, and that these molecules are homologues of the recited host-derived immune system inhibitors. As set forth in the specification on page 6, lines 7-22, infectious microorganisms are known in the art to produce molecules that are homologues of mammalian immune system inhibitors. The specification explicitly teaches that the specific homologues recited in Claim 11 are known in the art, and publications that described these homologues are referenced. Applicants submit that the meaning of the term "homologue" as used in Claim 11, is therefore not indefinite.

d. The Examiner contends that Claims 12, 14 and those dependent therefrom are indefinite because it is not clear what "binding partners" are encompassed by the phrase "naturally occurring."

Claims 12, 14 and those dependent therefrom have been amended to clarify that the phrase "naturally occurring binding partners" refers to a binding partner to which the targeted immune system inhibitor naturally binds (i.e., the binding partner to which the targeted immune system inhibitor binds in nature or *in vivo*). This meaning is set forth, for example, in the specification, page 11, line 27 to page 12, line 5; and page 16, line 26 to page 17, line 3.

e. The Examiner contends that Claim 13 is indefinite because it is allegedly not clear how a naturally occurring binding partner can be produced recombinantly.

In view of the amendment to Claim 12, from which Claim 13 depends, Applicants submit that it is clear how the recited binding partner can be produced recombinantly and this issue should be moot.

f. The Examiner contends that Claims 15, 18-23 and 25-27 are indefinite for reciting "fragments" because it is allegedly unclear if the term means antigen binding fragments or fragments that encompass single amino acids.

Claims 15, 18-23 and 25-27 have been amended to clarify that the term "fragments" is intended to refer to antigen binding fragments. Applicants note that the specification is clear that fragments are intended to selectively bind to the targeted immune system inhibitor, for example, on page 17, lines 3-7.

g. The Examiner contends that Claim 36 is indefinite for reciting "further comprising after step (a) the steps of," in that steps (a)-(d) in Claim 36 would be in between steps (a) and (b) in Claim 1, which the Examiner asserts makes no sense.

Applicants have canceled Claim 36, without prejudice to or disclaimer of the subject matter therein and therefore, this issue is believed to be moot.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3, 5, 10-27 and 34-43 under 35 U.S.C. § 112, second paragraph.

Objection to the Specification and Rejection of Claims 14-15, 18-23 and 25-27 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 14-15, 18-23 and 25-27 under 35 U.S.C. § 112, first paragraph, contending that the specification, while being enabling for antibodies and antibody[sic] fragments which specifically bind antigen, does not reasonably provide enablement for fragments of antibodies which would not bind antigen.

To more particularly describe the present invention, Applicants have amended Claims 14, 18, 20, 22, and 25-27 to clarify that the claimed antibodies and fragments thereof specifically bind to antigen (i.e., the targeted immune system inhibitor). Support for this amendment is found in the specification on page 16, line 24, through page 17, line 7.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 14-15, 18-23 and 25-27 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1-3, 5, 10-27 and 34-43 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1-3, 5, 10-27 and 34-43 under 35 U.S.C. § 103, contending that these claims are not patentable over Lentz (U.S. Patent 4,708,713) and further in view of Selinsky et al. and Maraskovsky et al. Specifically, the Examiner states that Lentz teaches a method and system for removing immunosuppressive components from the blood of mammals for treating diseases and conditions, whereby the treated blood is returned to the patient to initiate an immune response. In particular, the Examiner asserts that Lentz teaches the separation of blood cells from plasma, where the plasma is treated with immobilized protein A and returned to the patient. The Examiner admits that Lentz does not teach a monoclonal antibody specific for soluble receptors for TNFα and TNFβ covalently joined to a macroporous bead, but contends that these deficiencies are made up in the disclosures of Selinsky et al. and Maraskovsky et al. It is noted that TNFα and TNFβ bind to the same receptors, and that the claims and discussion reflect this point. Selinsky et al. is cited as allegedly teaching antibodies specific for soluble TNF receptor I (sTNFRI) and Ultrapheresis, and that sTNFRI is removed by Ultrapheresis. Selinsky et al. is further cited as demonstrating that sTNFRI effectively inhibits immune responses *in vivo* and for the statement: "We, therefore, propose the development of methods and/or reagents capable of specifically removing sTNFRI, or antagonizing its effects *in situ*, as unconventional, yet promising, strategies for cancer immunotherapy." Finally, Marakovsky et al. is cited as allegedly teaching a method of stimulating an immune response in a patient providing a method in which antibodies specific for antigens are immobilized on the surface of macroporous beads, where blood cells are collected by apheresis, where monoclonal antibodies remove specific cells, where the antibody-antigen complex is removed from the beads, and where the cells are administered to a patient. Therefore, the Examiner contends that it would have been *prima facie* obvious to combine the cited references to arrive at the present invention as claimed.

Applicants traverse the Examiner's rejection of Claims 1-3, 5, 10-27 and 34-43 under 35 U.S.C. § 103, and submit that the Examiner has not established a *prima facie* case of obviousness. Initially, Applicants note that for a *prima facie* case of obviousness to be established, the following three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings. Second, there must be a reasonable expectation of success. Third, the combination of references must teach or suggest all of the claim limitations.

Applicants submit that the combination of references does not meet all of the above-requirements for a case of *prima facie* obviousness. First, Applicants submit that the combination of references does not teach or suggest all of the claim limitations. Specifically, as the Examiner admits, Lentz does not teach a monoclonal antibody specific for soluble receptors for tumor necrosis factors α and β (TNFα and TNFβ) covalently joined to a macroporous bead. Applicants submit that not only does Lentz not teach these specific elements, Lentz does not teach or suggest any antibody or other binding partner that specifically binds to a specified target molecule and as such, can not teach an inert medium for binding to such a molecule. More importantly, Applicants submit that Lentz does not teach or suggest the *concept* of the present invention at all, which is the use of a specific binding partner to *selectively and specifically* remove targeted components from a bodily fluid for the purpose of producing an altered bodily fluid with enhanced immune stimulatory properties. Applicants submit that this is an important point, since the Examiner is obligated to view the claimed method as a whole, and not merely for the individual components which make up the method.

In addition, contrary to the Examiner's contention that Lentz teaches plasmapheresis to separate blood cells from plasma by treating plasma with immobilized protein A, Applicants respectfully note that this discussion in Lentz is a reference to a prior art method of non-specifically treating plasma to mitigate immune deficiency and is discouraged by Lentz. Specifically Lentz states that this method of separating plasma from the cellular portion of whole blood "has a serious impact on the platelet level in the blood," "could not be considered for widespread use," and is "not very attractive for clinical use." (See column 1, lines 51-62). Additionally, Lentz states that separation of the plasma from the blood is "not as efficient as the preferred embodiment" (col. 10, lines 2-4). Therefore, Applicants submit that Lentz can be viewed as a teaching away from a method which separates blood into a cellular and acellular component, and which uses a method other than ultrafiltration for removing components from blood.

Furthermore, Applicants do not agree that Selinsky et al. or Marakovsky et al., alone or in combination, make up for the deficiencies of Lentz. With regard to Selinsky et al., although Selinsky et al. use an antibody against TNFRI in *in vitro* experiments to evaluate the production of sTNFRI by recombinant cells and the effects of such production on TNF-induced lysis, Selinsky et al. do not teach the use of a binding partner including an antibody that selectively binds to an immune system inhibitor to selectively remove such an inhibitor from the acellular portion of a

biological fluid, nor any of the steps of the presently claimed method. Selinsky et al. state that the "therapeutic utility of manipulating sTNFRI levels *in vivo* has been demonstrated" (emphasis added) and that removing sTNFRI or antagonizing its effects *in situ* may be a promising strategy for cancer therapy; however, Selinsky et al. do not teach or suggest an *ex vivo* method for contacting an acellular portion of a bodily fluid such as blood with a binding agent that selectively binds to a targeted immune system inhibitor (including sTNFRI) such that the inhibitor is removed from the acellular portion, and then combining the altered acellular portion with the cellular portion of the fluid and returning the fluid to the animal from which it was obtained.

Marakovsky et al. do not make up for the deficiencies of the combination of Lentz and Selinsky et al. Marakovsky et al. teach a method for purifying stem cells or progenitor cells from an animal, such as by immunoaffinity chromatography with an antibody that binds to a cell surface marker on the cell, and then culturing the cells *in vitro* to differentiate the cells into dendritic cells. These purified and differentiated cells can then be administered to an animal as a type of adjuvant to stimulate an immune response in a patient. Marakovsky et al. do not teach or suggest separation of a bodily fluid into a cellular and acellular portion nor contacting the acellular portion with a binding agent that selectively binds to an immune system inhibitor. Therefore, Marakovsky et al. can not teach any of the additional steps of the claimed method of the present invention. More generally, the teachings of Marakovsky et al. differ from the present invention in that: (1) Marakovsky et al. is a method of *selecting for* a desired *cellular component* present in a bodily fluid (i.e., the purified cell is the target product), whereas the present invention is a method of *selecting against* an undesirable *acellular component* present in a bodily fluid (i.e., the altered bodily fluid is the target product); and, (2) the component isolated by the immunoaffinity column of Marakovsky et al. (i.e., stem cells) is ultimately *used* as an *adjuvant*, whereas the component removed by the binding partner of the present invention is ultimately *discarded* because it is an *inhibitor* of immune responses. Therefore, for the Examiner to correlate the method of stimulating the immune response of Marakovsky et al. with the present method is inaccurate, because Marakovsky et al. provide an exogenous source of immune stimulator to a patient, whereas the present method removes an inhibitor from a patient, thereby enhancing the ability of an endogenous immune stimulator to operate in the patient.

Moreover, Applicants submit that one of ordinary skill in the art would not have a reasonable expectation of success at practicing the claimed invention based on the cited combination of

references. First, Applicants refer to the above-discussion of Lentz and again submit that Lentz clearly *discourages* one of skill in the art from separating plasma from the cellular portion of whole blood, thus leading one of skill in the art to believe that the separation of cellular and acellular components as a step in the removal of components from the blood could actually be detrimental to a patient. This is a clear teaching away from the present invention in Lentz. Neither of Selinsky et al. or Marakovsky et al. teach a separation of acellular and cellular components of a bodily fluid, and so one of skill in the art is left with the expectation that such a step would be detrimental to a patient.

On this point, Applicants submit that, contrary to the teachings of Lentz against separating the acellular fraction from the cellular fraction prior to treatment of the bodily fluid, it is believed to be a significant advantage of the present invention to treat the acellular component of the bodily fluid separately from the cellular component. Specifically, certain of the molecules targeted for removal by the method of the present invention are soluble components which are typically characterized in that they bind to an immune stimulator. These soluble components often are homologues of *another* binding partner for the immune stimulator, such that the interaction between the immune stimulator and the other binding partner is inhibited by the binding of the soluble component to the immune stimulator. Since the other binding partner is frequently a cell-associated binding partner (e.g., is present on cell surfaces), it is desirable, and indeed, may be critical, to bind the soluble immune system inhibitor *without binding the homologous cell-associated binding partner*. For example, sTNFRI is a soluble receptor for TNFα and TNFβ, which is produced through a proteolytic cleavage of the membrane receptor (mTNFRI) for TNFα and β. This proteolysis releases the extracellular domain of the mTNFRI from the cell surface and allows it to diffuse freely into the extracellular space. The sTNFRI, thus produced, retains fully the ability to bind TNF α and β with high affinity. Binding of TNFα and β by the sTNFRI prevents TNFα and β from binding the mTNFRI. Consequently, the pro-inflammatory and apoptotic effects normally induced through the crosslinking of mTNFRI by TNFα and β also are inhibited. Due to the significant homology between sTNFRI and mTNFRI, contact of whole blood with a binding partner reactive with sTNFRI would permit binding to both the sTNFRI *and* the mTNFRI present on cell surfaces. This would have dire consequences for the patient, and would contradict the goals of the present method for several reasons. First, binding of the binding partner to mTNFRI would block its engagement by TNFα and β, thus, effectively reducing TNF-induced immune responses. Second, binding of an immobilized binding partner to mTNFRI would effect the depletion of mTNFRI-bearing leukocytes

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from whole blood, thereby diminishing immune competence. Third, and most undesirable, binding of an immobilized binding partner to mTNFRI would crosslink the receptor and act, therefore, as an agonist of TNFα and β. This would produce very significant and potentially fatal toxicities similar to those observed in human clinical trials of infusional TNFα. In summary, based on the teachings of Lentz, one of skill in the art would avoid separating whole blood into acellular and cellular components prior to practicing the present method. At best, this would significantly reduce or even eliminate the therapeutic benefit achieved by the present method and, at worst, would induce toxicities of profound magnitude. In fact, to be able to practice the present method when the targeted immune system inhibitor also occurs as a cell surface (e.g., membrane) molecule (e.g., sTNFRI and mTNFRI) *without* the separation of blood into cellular and acellular fractions, would require that the binding partner utilized be able to distinguish between the soluble and cell surface (membrane) forms of the molecule. For example, since sTNFRI derives from, and therefore is virtually identical to, the extracellular domain of mTNFRI, development of such a binding partner would be an extremely demanding technical feat, if it were at all possible. Currently, such a binding partner is not known in the art. Therefore, the present invention, which requires treating an acellular fraction of blood, allows for the selective removal of a specific component from the blood without the need to develop binding partners that distinguish between a soluble immune system inhibitor and its cell surface counterpart.

Finally, Applicants submit that the cited references fail to provide the requisite motivation to make the combination of references as the Examiner has done. Applicants refer again to the discussion above and submit that the Lentz and Marakovsky et al. patents are devoid of any suggestion of a method to stimulate an immune response by using an antigen-specific binding partner to selectively remove a specified immune system inhibitor from a bodily fluid, including from the acellular portion of a bodily fluid. Indeed, Lentz actually teaches away from the present invention, by discouraging the use of other methods, including those which include the separation of plasma from cellular components. As discussed above, the entire concept of Marakovsky is completely different from that of the present method, and so it is inconceivable that Marakovsky et al. could provide the motivation to arrive at the present invention.

In arguing that the comment in Selinsky et al. proposing the development of methods and/or reagents capable of specifically removing sTNFRI or antagonizing its effects *in situ*, is a basis for one of skill in the art to make and use the present invention, it appears that the Examiner is stating

that it would have been "obvious to try" modifying various parameters, and indeed creating an entire protocol *without any guidance* from Selinsky et al. (or Lentz or Marakovsky et al.), in order to produce the claimed invention. The Federal Circuit has provided clear direction with respect to arguments based on an "obvious to try" theory. The court has held that an "obvious to try" situation exists when a general disclosure may pique a scientist's curiosity, such that further investigation might be done as the result of a disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. In re Eli Lilly & Co., 14 USPQ 2d 1741, 1743 (Fed.Cir. 1990). The court held, however, that "obvious to try" is not to be equated with obviousness under 35 U.S.C. §103. See Gillette Co. v. S.C. Johnson & Son, Inc., 16 USPQ 2d 1923, 1928 (Fed.Cir. 1990). In this case, even if, *arguendo*, the disclosure of Selinsky et al. may pique the curiosity of one of skill in the art to consider how to antagonize or remove sTNFRI *in situ*, Selinsky et al. provide absolutely no guidance as to how one of skill in the art would be expected to go about such a task. Therefore, Selinsky et al. do not contain "a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." As discussed above, neither of Lentz or Marakovsky et al. makes up for the deficiency of teachings in Selinsky et al.

Therefore, it appears that in the present case the only suggestion for the Examiner's combination of the teachings in the cited references improperly stems from the Applicants' own disclosure and not from the cited references themselves. At best, the Examiner's comments regarding obviousness appear to amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at Applicants' invention because they would have had the necessary skills to carry out the requisite process steps. This is an inappropriate standard for obviousness. "A statement that modifications of the prior art to meet the claim limitations would have been 'well within the ordinary skill of the art at the time the invention was made', because the cited references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993)." MPEP 2143.01. Applicants submit that none of the references, alone or in combination, provide an impetus necessary to cause one skilled in the art to combine the teachings of the references in the way the Examiner has done.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3, 5, 10-27 and 34-43 under 35 U.S.C. § 103.

Applicants have attempted to address all of the Examiner's concerns in the August 18 Office Action. In the event that the Examiner has any questions regarding Applicants' position, the Examiner is invited to contact the below-named agent at (303) 863-9700.

Respectfully submitted,

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